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(WO/1999/034831) ENHANCED TRANSPORT USING MEMBRANE DISRUPTIVE AGENTS

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Priority Data: **60/070,411 05.01.1998 US**

Title: **ENHANCED TRANSPORT USING MEMBRANE DISRUPTIVE AGENTS**

Abstract: Compositions and methods for transport or release of therapeutic and diagnostic agents or metabolites or other analytes from cells, compartments within cells, or through cell layers or barriers are described. The compositions include a membrane barrier transport enhancing agent and are usually administered in combination with an enhancer and/or exposure to stimuli to effect disruption or altered permeability, transport or release. In a preferred embodiment, the compositions include compounds which disrupt endosomal membranes in response to the low pH in the endosomes but which are relatively inactive toward cell membranes, coupled directly or indirectly to a therapeutic or diagnostic agent. Other disruptive agents can also be used, responsive to stimuli and/or enhancers other than pH, such as light, electrical stimuli, electromagnetic stimuli, ultrasound, temperature, or combinations thereof. The compounds can be coupled by ionic, covalent or H bonds to an agent to be delivered or to a ligand which forms a complex with the agent to be delivered. Agents to be delivered can be therapeutic and/or diagnostic agents. Treatments which enhance delivery such as ultrasound, iontophoresis, and/or electrophoresis can also be used with the disrupting agents.

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Compositions and methods for transport or release of therapeutic and diagnostic agents or metabolites or other analytes from cells, compartments within cells, or through cell layers or barriers are described. The compositions include a membrane barrier transport enhancing agent and are usually administered in combination with an enhancer and/or exposure to stimuli to effect disruption or altered permeability, transport or release. In a preferred embodiment, the compositions include compounds which disrupt endosomal membranes in response to the low pH in the endosomes but which are relatively inactive toward cell membranes, coupled directly or indirectly to a therapeutic or diagnostic agent. Other disruptive agents can also be used, responsive to stimuli and/or enhancers other than pH, such as light, electrical stimuli, electromagnetic stimuli, ultrasound, temperature, or combinations thereof. The compounds can be coupled by ionic, covalent or H bonds to an agent to be delivered or to a ligand which forms a complex with the agent to be delivered. Agents to be delivered can be therapeutic and/or diagnostic agents. Treatments which enhance delivery such as ultrasound, iontophoresis, and/or electrophoresis can also be used with the disrupting agents.

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